

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020801

Trade Name: PEPCID AC CHEWABLE TABLETS

Generic Name: FAMOTIDINE

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 09/24/98

**Indication(s): TREATMENT OR PREVENTION OF
MEAL-INDUCED HEARTBURN, ACID INDIGESTION,
AND SOUR STOMACH**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020801

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	Included	Pending Completion	Not Prepared	Not Required
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020801

APPROVAL LETTER



NDA 20-801

SEP 24 1998

Merck Research Laboratories
Attention: George Latyszonek
Director, Regulatory Affairs
Sumneytown Pike, BLA-20
West Point, PA 19486

Dear Mr. Latyszonek:

Please refer to your new drug application (NDA) dated December 18, 1996, received December 19, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid AC (famotidine) Chewable Tablets.

We acknowledge receipt of your submissions dated August 21 and September 11 and 24, 1998. The August 21, 1998 submission, received on August 24, 1998, constituted a full response to our August 5, 1998 action letter. The user fee goal date for this application is October 24, 1998.

This new drug application provides for a chewable tablet dosage form of nonprescription Pepcid AC (famotidine) for the treatment or prevention of meal-induced heartburn, acid indigestion, and sour stomach.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labels submitted on August 21, 1998). Accordingly, the application is approved effective on the date of this letter.

We remind you of the commitment stated in your submission dated September 24, 1998, to revise the labeling for the drug product by December 7, 1998, to include the following warning:

"Allergy Warning: Do not use if you are allergic to Pepcid AC (famotidine) or other acid reducers."

In addition, we remind you of the commitment made in your submission dated August 21, 1998, to revise the labeling for the drug product within six months as follows:

1. Revise the statements in the **USES** section as follows to denote heartburn as the primary symptom, with the other symptoms as secondary symptoms:
 - "For relief of heartburn associated with acid indigestion and sour stomach;"
 - "For prevention of heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages."

Do not bold or underline any word or statement in this section.

2. Regarding the **DIRECTIONS** section on all labeling components, bold only the following words or phrase: "relieve", "prevent", and "60 minutes before".
3. Regarding the **WARNINGS** section on all labeling components, move the pregnancy/nursing warning statement to immediately before the "Keep this and all drugs out of reach of children." warning statement.
4. Concerning the first and second bullet statements at the top of the back panel of the carton and pouch dispenser:
 - a. Remove all underlining from these statements.
 - b. To be consistent with the statement in the **READ THE LABEL** section of the label, revise the phrase "(Read Consumer Leaflet before use)" in the first bullet to "(Read Package Insert before use)." In addition, consider including the text "Package Insert" on the front panel of the package insert labeling to make it easier for consumers to identify this document.
5. Revise the third bullet statement under the "Tips for Managing Heartburn" in the labeling to: "Certain foods or drinks are more likely to cause heartburn, such as rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, and even some fruits and vegetables."

6. Regarding the Tamper Resistant/Tamper Evident Statements:

- a. On the back panel of the pouch, revise this Statement "Do not use if pouch is open or broken" by replacing the word "broken" with "torn." In addition, move this statement from the "WARNINGS" section to either near the diagonal phrase "While folded on line, tear open at slit" or immediately before the phrase "READ THE DIRECTIONS AND WARNINGS BEFORE USE."
- b. Revise this statement, "Do not use if the individual pouch is open or broken," on the back panel of the carton and dispenser and on the front page of the package insert to read "Do not use if the individual pouch is open or torn."
- c. Revise the font for all of these statements from all upper case to upper and lower case.

In addition, we request that you consider reformatting the labeling as outlined in the February 27, 1997, Federal Register Notice "Over-the-Counter Human Drugs; Proposed Labeling Requirements" [62 FR 9023].

Please submit 20 copies of the revised final printed labeling (FPL) as a "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c).

Finally, validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit four copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Gastrointestinal and Coagulation Drug Products, one to the Division of Over-the-Counter Drug Products, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

In line with Center for Drug Evaluation and Research policy, oversight of this application is being transferred to the Division of Over-the-Counter Drug Products. If you have any questions, contact Albert Rothschild, Project Manager, at (301) 827-2222.

Sincerely,

/s/

/s/

✓ Debra Bowen, M.D.
Acting Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

APPROVABLE LETTER

Case/Followed

NDA 20-801

Merck Research Laboratories
Attention: George Latyszonek
Director, Regulatory Affairs
Sumneytown Pike, BLA-20
West Point, PA 19486

AUG - 5 1998

Dear Mr. Latyszonek:

Please refer to your new drug application (NDA) dated December 18, 1996, received December 19, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid® AC (famotidine) Chewable Tablets.

We acknowledge receipt of your submissions dated February 5; March 6; May 1 and 27; and June 9, 1998. Your submission of February 5, 1998 constituted a full response to our December 19, 1997, action letter. The user fee goal date for this application is August 6, 1998.

We have completed the review of this application, as amended with draft labeling submitted on February 5, 1998, and it is approvable. Before this application can be approved, however, a satisfactory Establishment Inspection Report must be received for all manufacturing facilities. During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector.

In addition, it will be necessary for you to revise the labeling as follows:

1. The proposal to change the trade name for the drug product from "Pepcid® AC Acid Controller" to "Pepcid® AC" was found acceptable. All labeling components for all dosage forms for this drug should be revised to reflect this new trade name.
2. Revise the statements in the USES section as follows to denote heartburn as the primary symptom, with the other symptoms as secondary symptoms:
 - "For relief of heartburn associated with acid indigestion and sour stomach;"
 - "For prevention of heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages."

Do not bold or underline any word or statement in this section.

3. Regarding the **DIRECTIONS** section on all labeling components:
 - a. Bold only the following words or phrase: “**relieve**”, “**prevent**”, and “**60 minutes before**”.
 - b. Concerning our December 19, 1998 request to revise the **DIRECTIONS** section to state that the drug be taken with “a full glass of water,” we believe that the use of a full glass of water is appropriate to increase the likelihood that an adequate volume of fluid is ingested to ensure proper esophageal transit, disintegration and dissolution of the medication. However, after considering your response to our request, we conclude that it is acceptable to revise this phrase to “...swallow with a glass of water.”

4. Regarding the **WARNINGS** section on all labeling components:
 - a. Include the following allergy warning-statement as the first warning statement: “Do not use if you are allergic to Pepcid AC (famotidine) or other acid reducers.”
 - b. Move the pregnancy/nursing warning statement to immediately before the “Keep this and all drugs out of reach of children.” warning statement.

5. Concerning the first and second bullet statements at the top of the back panel of the carton and pouch dispenser:
 - a. Remove all underlining from these statements.
 - b. To be consistent with the statement in the **READ THE LABEL** section of the label, revise the phrase “(Read Consumer Leaflet before use)” in the first bullet to “(Read Package Insert before use).” In addition, consider including the text “Package Insert” on the front panel of the package insert labeling to make it easier for consumers to identify this document.

6. Since the December 19, 1997, action letter, the third bullet statement under the “Tips for Managing Heartburn” on acid reducer product labeling has been modified and simplified. For consistency, revise this bullet statement on all labeling to: “Certain foods or drinks are more likely to cause heartburn, such as rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, and even some fruits and vegetables.”

7. Regarding the Tamper Resistant/Tamper Evident Statements:

- a. On the back panel of the pouch, revise this Statement "Do not use if pouch is open or broken" by replacing the word "broken" with "torn." In addition, move this statement from the "WARNINGS" section to either near the diagonal phrase "While folded on line, tear open at slit" or immediately before the phrase "READ THE DIRECTIONS AND WARNINGS BEFORE USE."
- b. Revise this statement, "Do not use if the individual pouch is open or broken," on the back panel of the carton and dispenser and on the front page of the package insert to read "Do not use if the individual pouch is open or torn."
- c. Revise the font for all of these statements from all upper case to upper and lower case.

8. Regarding the storage statement and expiry period:

- a. As committed to in your June 9, 1998, submission, revise the storage statement on all labeling for this drug product to "Store at 25°C (77°F); Excursions permitted to 15°-30°C (59°-86°F)."
- b. Be advised that the data submitted to date supports an expiry period of 36 months.

Finally, we request that you consider reformatting the labeling as outlined in the February 27, 1997, Federal Register Notice "Over-the-Counter Human Drugs; Proposed Labeling Requirements" [62 FR 9023].

Please submit 20 copies of the final printed labeling, ten of which individually mounted on heavy weight paper or similar material, as well as an image of the labeling for the carton and package insert on diskette in PDF (Adobe Acrobat) format. If additional information relating to the safety or effectiveness of this drug becomes available or if the February 27, 1997, Federal Register Notice "Over-the-Counter Human Drugs; Proposed Labeling Requirements" [62 FR 9023] becomes final before this application is approved, revision of that labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

NDA 20-801

Page 4

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Michael Folkendt, Regulatory Project Manager, at (301) 443-0487.

Sincerely,

/S/ 8-5-98

Debra Bowen, M.D.
Acting Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/S/ 8-5-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

MEDICAL REVIEW(S)

J. J. Kendt

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW**

JUN - 1 1998

NDA: ^{AZ} 20-801 (ASL)

Sponsor: Merck Research Laboratories

Drug name: Nonprescription Famotidine Chewable Tablets
10mg

Date submitted: February 5, 1998

Date received: February 6, 1998

Date received by Medical Officer: February 12, 1998

Review completed: May 29, 1998

Reviewer: Kathy M. Robie-Suh, M.D., Ph.D.

Famotidine 10mg is currently marketed over-the-counter as a swallow tablet formulation (Pepcid AC Acid Controller) for the treatment and prevention of heartburn symptoms (initial approval 4/28/95). The sponsor proposes marketing a chewable formulation of the drug. Clinical studies submitted by the sponsor demonstrated bioequivalence of the proposed chewable formulation to the marketed formulation and accordingly the sponsor was sent an approvable letter on December 19, 1997. In the current submission the sponsor responds to the approvable letter.

- The current submission consists of two volumes containing:
- requested reanalysis of Protocol #036 bioequivalence study data
 - additional Chemistry Manufacturing and Controls (CMC) information
 - revised draft labeling

I have reviewed the revised draft labeling.

Reviewer's Comments on Labeling:

Specific comments:

1. The sponsor proposes to change the product line name from . This change is acceptable. The statement of identity ("famotidine 10mg/acid reducer") which appears below the product name on the box and package insert provides the same information to the consumer about the pharmacologic action of the drug.
2. In the approvable letter the sponsor was requested to change the directions statement from
This recommendation was made by the Division of Over-the-

Counter Drug Products because of concerns about the small tablet as a choking hazard.

The sponsor points out that the bioequivalence trials for the chewable formulation used only 4-5 ounces of water and the clinical trials for the film-coated tablets either did not specify an amount of water or specified 3-4 ounces. The clinical data do not support recommending any specific amount of water to be taken with either the film-coated or chewable tablets. No adverse events related to swallowing the tablets were reported in any of the clinical studies and by my examination of the FDA ADRIS spontaneous reports safety data base, there do not appear to be any reports of choking with OTC famotidine. Therefore, the sponsor's proposed language should be acceptable.

Conclusions and Recommendations:

From a clinical point-of-view the sponsor's proposed labeling is acceptable.

/S/

APPEARS THIS WAY
ON ORIGINAL

Kathy M. Robie-Suh, M.D., Ph.D.

5/29/98

cc:

NDA 20-801

HFD-180/Division File

HFD-180/LTalarico

HFD-180/KRobie-Suh

HFD-180/MFolkendt

HFD-180/JChoudary

HFD-180/EDuffy

HFD-560/DBowen

HFD-560/LKatz

HFD-560/ARothschild

f/t 5/29/98 krs

MED\N\20801805.OKR

/S/

6-1-98

APPEARS THIS WAY
ON ORIGINAL

John Kendt

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW**

OCT - 8 1997

NDA: 20-801

Sponsor: Merck Research Laboratories

Drug name: Nonprescription Famotidine Chewable Tablets 10mg

Date submitted: December 18, 1996

Date received: December 19, 1996

Date received by Medical Officer: May 28, 1997

Review completed: October 6, 1997

Reviewer: Kathy M. Robie-Suh, M.D., Ph.D.

APPEARS TO BE
ON ORIGINALLY

Background:

Famotidine 10mg as a swallow tablet formulation (Pepcid AC Acid Controller) currently is marketed over-the-counter for treatment and prevention of heartburn symptoms (initial approval 4/28/95). In this submission the sponsor proposes a chewable formulation of famotidine 10mg for the currently approved over-the-counter indications. The sponsor claims efficacy of the new formulation based on demonstration of bioequivalence to the already approved product. The supporting bioequivalence studies are included in this application.

Current labeling for nonprescription famotidine is attached to this review as Appendix A.

Materials Reviewed:

This submission consists of the following:

- Vol. 1:1 Index, Synopsis of Application, Annotated Labeling
- Vols. 1.2 and 1.3 Chemical and Pharmaceutical Manufacturing and Control Documentation
- Vol. 1.4 Samples, Methods Validation and Labeling
- Vol. 1.5 and 1.6 Human Pharmacokinetics and Bioavailability Documentation
- Vols. 1.7 through 1.9 Clinical Documentation
- Vols. 1.10 through 1.12 Statistical Documentation
- Vol. 1.13 Case Report Form Tabulations

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Because efficacy for the chewable formulation is being claimed based on bioequivalence of the chewable formulation to the already marketed tablet formulation, no clinical evidence for efficacy is presented in this submission. The clinical studies reported in full in this submission consist of two pharmacokinetic/bioequivalence studies (Studies 036 and 089), which are being reviewed by FDA Biopharmaceutics..

In addition, safety information from two clinical efficacy trials (Studies 078 and 079) is submitted. These randomized, placebo-controlled, parallel group studies were a multi-

center (078) trial and a single-center (079) trial to compare effectiveness of the chewable formulation, and two strengths of antacid versus placebo in relieving heartburn symptoms resulting from a provocative meal. According to the sponsor these two studies "are part of an independent development program and reports have not yet been completed" and the complete reports are not included in the current application. [Note: Heartburn severity efficacy data from Study 078 is included in the data tabulations, but no summary or analysis of the data is included]. Safety information from Study 073, a drug interaction study, also is submitted.

This submission contains no case report forms, because no patients died or were discontinued from study because of adverse events.

For this review I have examined information in volumes 1.1, 1.7 through 1.9 and 1.13.

Chemistry, Manufacturing and Control Information:

The compositions of the proposed and already marketed formulations of OTC famotidine are shown in the table below:

Compositions of Marketed OTC Famotidine 10mg and Proposed Chewable Famotidine 10mg

Ingredient	Milligrams per Tablet	
	Chewable Tablet	
Famotidine	10.00	
Lactose		
Hydroxypropyl Methylcellulose		
Microcrystalline Cellulose		
Magnesium Stearate		
Cellulose Acetate		
Hydroxypropyl Cellulose		
Mannitol		
Aspartame		
Red Ferric Oxide NF		
Total Tablet Weight		

*Removed during processing.

Clinical Pharmacology:

Famotidine is a competitive histamine H₂-receptor antagonist. It inhibits basal and nocturnal gastric acid secretion and food or pentagastrin induced gastric acid secretion in normal people and in hypersecretors.

Famotidine exhibits linear pharmacokinetics over the dose range studied (5 to 40mg). About 71% of an intravenous dose of famotidine appears unchanged in the urine. Upon oral administration, about 38% of the dose is found in the urine and 51% in the feces. The only identified metabolite of famotidine is the S-oxide. The half-life following intravenous or oral administration is about 2.8 hours in healthy young individuals. The half-life increases disproportionately with renal impairment.

Bioavailability of famotidine from prescription dose Pepcid tablets (20mg and 40mg) is about 42%. Famotidine is not extensively bound to plasma protein. Famotidine does not have a high affinity for interaction with cytochrome P-450 and does not significantly affect the pharmacokinetics of drugs (such as diazepam, theophylline, and phenytoin) metabolized by cytochrome P-450 systems.

According to the sponsor, bioequivalence Studies 036 and 089 show the proposed 10mg chewable tablet to be bioequivalent to the marketed tablet formulation. A summary description of these studies' design and results is given in the sponsor's Table C2 (NDA Vol. 1.7 p. C-10) which is attached to this review as Appendix B.

Clinical Safety Summary:

Clinical investigations of famotidine chewable tablets have involved a total of 709 subjects. These include subjects in 5 studies. Studies 036 and 089 were bioequivalence trials; Study 073 was a drug interaction study; and Studies 078 and 079 were pilot clinical efficacy trials. In these 5 studies 234 subjects received the famotidine chewable tablet. Each subject received only a single dose of study medication. Numbers of subjects treated in these studies are summarized in the following table:

Number of Subjects Treated in All Clinical Studies

Treatment Group	Protocol Number					Total
	036 ^c	073 ^c	078 ^a	079 ^a	089 ^c	
Famotidine CCT	15	17	118	60	24	234
Famotidine	15				24	39
Famotidine Effervescent	15					15
Famotidine CCT & Antacid 42mEq ANC		16 ^{**}				16
Antacid 42mEq ANC			118	59 [*]		177
Antacid 21mEq ANC			119			119
Placebo			119	60		179
Total	15	17	474	179	24	709

^{*} Does not include subject who was randomized to CCT (AN91) but also took antacid 42mEq (AN94).
^{**} One subject completed only one period.
^c Crossover Study Design
^a Parallel Study Design

Patients in these studies were mostly women (63%) and mean age was 36 years (median, 35yrs). Only 2% of patients were older than 64 years and there were no pediatric patients. Sixty percent of patients were White, 21% were Black and 18% were Hispanic.

There were no adverse events in Study 036, a single-dose cross-over bioequivalence trial in 15 subjects, or in Study 073, an investigation of possible interaction between famotidine 10mg chewable tablets and calcium carbonate-magnesium hydroxide chewable tablets. In Study 089, a single-dose cross-over bioequivalence trial involving 24 subjects, four subjects had adverse events: One subject experienced lightheadedness and a rash (judged possibly study drug related), another developed herpes simplex on the lip, another experienced pruritus and a rash on one arm, and one had rhinorrhea. All patients completed the study.

Among patients in the single-center clinical efficacy Study 079, of the 179 patients randomized, only one patient (receiving antacid 42MEq) reported adverse event (dizziness and headache). Twenty-five (14%) of the 179 patients enrolled in Study 079 were discontinued from the study because of having heartburn prior to the provocative meal. One patient in the famotidine 10mg chewable tablet group was discontinued because of a protocol violation.

In the multi-center clinical efficacy trial, Study 078, adverse events were reported in 44 of the 474 patients randomized (9.3% of famotidine chewable; 13.6% of antacid 42mEq ANC, 4.2% of antacid 21mEq ANC, and 10.1% of placebo patients). The most frequent adverse event in patients receiving the famotidine 10mg chewable tablet was headache (7 patients (5.9%)). Other events occurring in this group included chest pain, hypertension, palpitation, nausea and vomiting, each of which occurred in only one patient. In the antacid and placebo groups diarrhea occurred in about 3% of patients and headache in about 3%. Events judged to be possibly related to study drug are summarized in the table below. (No events were judged to be probably, likely or definitely related to study drug).

Study 078: Adverse Events Possibly Related to Study Drug

Event	Number of Patients (%)			
	Placebo	Famotidine 10mg Chewable Tab	Antacid 21 MEq ANC	Antacid 42mEq ANC
	n=119	n=118	n=119	n=118
Diarrhea	6 (5.0%)	0	1 (0.8%)	7 (5.9%)
Headache	1 (0.8%)	3 (2.5%)	1 (0.8%)	2 (1.7%)
Constipation	0	1 (0.8%)	0	0
Dream Abnormality	1 (0.8%)	0	0	0
Nausea	1 (0.8%)	0	1 (0.8%)	1 (0.8%)
Abdominal Pain	0	0	0	1 (0.8%)

reviewer's original table, based on information in sponsor's tables, NDA Vol. 1.9, pp. D-199 through D-207.

One patient in this study, a 42 year old man with no history of medical problems, assigned to the famotidine 10mg chewable tablet group, experienced serious adverse events (hypertension, chest pain, and palpitations for which he was hospitalized); these events were felt probably not related to study drug. All randomized patients completed the study.

The safety of the famotidine 10mg chewable product is further supported by the safety information for the famotidine 10mg tablet formulation (NDA 20-325). (See my Medical Officer's Reviews dated 1/12/94 and 6/13/94).

Reviewer's Comments and Discussion:

The safety database for famotidine 10mg is adequate to support the marketing of the proposed chewable tablet formulation of famotidine.

The sponsor has provided annotated labeling for the proposed chewable product. The labeling for the chewable formulation should be the same as for the marketed formulation except

- the dosing instruction should say
- information about the chemical composition of the chewable tablet, including potential phenylalanine content should be included,
- A statement in the Clinical Studies section indicates that the chewable tablets have been shown to be bioequivalent to the swallow tablets.

Conclusions and Recommendations:

From a clinical point-of-view the proposed application is approvable and the proposed labeling is acceptable, provided FDA Biopharmaceutics concludes that the chewable formulation is bioequivalent to the marketed OTC famotidine 10mg tablet formulation.

/S/

**APPEARS THIS WAY
ON ORIGINAL**

Kathy M. Robie-Suh, M.D., Ph.D. 10/8/97

- cc:
- NDA 20-801
 - HFD-180
 - HFD-180/LTalarico **/S/** 10-8-97
 - HFD-180/KRobie-Suh
 - HFD-180/CSO
 - HFD-180/JChoudary
 - HFD-180/EDuffy
 - HFD-720/Biometrics
 - f/t 10/8/97 jgw
 - MED\N\20801710.OKR

**APPEARS THIS WAY
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APPENDIX A

3 Page(s) Redacted

DRAFTING LABELING

APPENDIX B

Nonprescription Famotidine 10-mg Chewable Tablets
 Clinical Documentation
 C. Clinical Pharmacology
 I. Summary

B. Table of Investigations (Cont.)

Table C-2 Table of Investigations

Study No. [Ref]	Objective	Dosages/ Study Design	Formulations: Lot Number and Batch Size	Results
036 [C-5]	To evaluate the bioequivalence of the 10-mg CCT formulation to the 10-mg FCT formulation. (The bioequivalence of an experimental effervescent formulation was also examined in the study, data of which not presented in the NDA).	Open-label, randomized, three-period crossover, single-dose study in 15 healthy male volunteers. The FCT dose was administered with 150 mL water. The CCT dose was administered with 150 mL water after the dose was chewed.	FCT: 0208-FCT-038-D001; Batch size: CCT: 0208-OTC-044-B002; Batch size:	The geometric mean AUC was 247.9 ng•hr/mL for the CCT formulation and 251.6 ng•hr/mL for the FCT formulation. The bioavailability of CCT relative to that of FCT averaged (Geometric Mean) 0.98 with a 90% CI of (0.86, 1.11). The C_{max} and T_{max} averaged (mean±S.D.) 40.0±17.4 ng/mL and 2.2±0.8 hr for CCT and 41.1±16.4 ng/mL and 2.0±0.7 hr for FCT, respectively. The ratio of C_{max} of CCT (geometric mean = 36.9 ng/mL) to FCT (geometric mean = 38.7 ng/mL) averaged 0.94 with a 90% CI of (0.80, 1.11). These data indicate the two formulations are bioequivalent.
089 [C-6]	To assess the bioequivalence of the slow-dissolving batch of the 10-mg CCT formulation to the 10-mg FCT formulation.	Open-label, randomized, two-period crossover, single-dose study in 24 healthy fasting volunteers (10M, 14F). The FCT dose was administered with 120 mL water. The CCT dose was administered with 120 mL water after the dose was chewed.	FCT: 2035480 (SBH141); batch size = CCT: RX214526 (C-402-2J); batch size:	The geometric mean AUC was 228.0 ng•hr/mL for the CCT formulation and 229.2 ng•hr/mL for the FCT formulation. The bioavailability of CCT relative to that of FCT averaged (Geometric Mean) 0.99 with a 90% CI of (0.90, 1.10). The C_{max} and T_{max} averaged (mean±S.D.) 42.5±15.1 ng/mL and 2.2±0.8 hr for CCT and 43.1±18.6 ng/mL and 1.9±0.8 hr for FCT, respectively. The ratio of C_{max} of CCT (geometric mean = 39.4 ng/mL) to FCT (geometric mean = 40.5 ng/mL) averaged 0.97 with a 90% CI of (0.87, 1.09). These data indicate the two formulations are bioequivalent.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

CHEMISTRY REVIEW(S)

Falkenberg

JUL 14 1998

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-801

CHEM. REVIEW #2 REVIEW DATE: 6/19/1998

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	02/05/1998	02/06/1998	02/13/1998
Amendment	05/01/1998	05/04/1998	05/08/1998
Amendment	05/27/1998	05/29/1998	06/08/1998
Amendment	06/09/1998	06/10/1998	06/18/1998

NAME & ADDRESS OF APPLICANT:

Merck Research Laboratories
Sumneytown Pike, BLA-20
West Point, PA 19486

DRUG PRODUCT NAME

<u>Proprietary:</u>	PEPCID® Acid Controller™
<u>Nonproprietary/USAN:</u>	Famotidine
<u>Code Name/#:</u>	MK-0208
<u>Chem. Type/Ther. Class:</u>	3S

PHARMACOL. CATEGORY/INDICATION:

Antagonist (to histamine H₂ receptors)/Prevention and Treatment of Heartburn

DOSAGE FORM:

Chewable Tablets

STRENGTHS:

10 mg

ROUTE OF ADMINISTRATION:

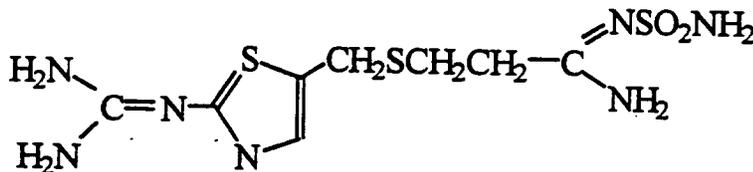
Oral

DISPENSED:

_____ Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:

1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propylidene)sulfamide



Molecular Formula: C₈H₁₅N₇O₂S₃

Molecular Weight: 337.43

SUPPORTING DOCUMENTS:

Document No. and holder name	Item to be reviewed	Notes
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NDA 20-235 Merck	Famotidine tablets	Approved NDA
NDA 19-462 Merck	NDA (drug substance famotidine)	Approved NDA
NDA 20-752 Merck	NDA (Pepcid® RPD tablets)	Approved NDA

RELATED DOCUMENTS (if applicable):

NDA 19-462 (Tablets PEPCID® prescription strength)
NDA 20-325 (Pepcid® AC Acid Controller™ Tablets)

CONSULTS: Biopharmaceutics reviewer concluded that the application is acceptable
Statistical analysis concludes 24 months expiry.

REMARKS/COMMENTS:

- Amendment, dated 2/5/1998, contains Merck Research Laboratories responses to our chemistry deficiencies and comments which were included in the approvable letter dated December 10, 1997.
- Amendment dated 6/9/1998 contains the revised storage statement for the drug product (store at 25°C (77°F); Excursion permitted to 15-30°C (59-86°F)). This statement is one of two options presented to the firm by the agency in our teleconference with the firm on 6/1/1998. The other statement, which firm did not accept, is Store at 25-30°C (77-86°F).
- The Carton and the Dispenser contain the appropriate storage conditions. All other labeling related items were dealt with by the Labeling and Nomenclature Committee and by the Division of OTC drug products.
- Amendment dated 5/4/1998 contains clarification from the firm regarding the requested expiration dating and statistical analysis of the stability data. This information was requested by the statistical reviewer via a teleconference with the firm on April 16, 1998.
- Regarding the statistical reviewer, Dr. Wen-Jen Chen, recommends 24 months expiration dating for Pepcid® AC drug product
- The Clinical Pharmacology and Biopharmaceutical Review concluded that the application is acceptable.
- Recent EER dated June 30, 1998 indicated that the Packaging Coordinators site needs to be reinspected.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The amendments contain satisfactory responses to our chemistry deficiency and comments, which were included in the approvable letter dated December 10, 1997. However, the recent CDER Establishment Evaluation Report indicated that Packaging Coordinators site needs to be reinspected, and the Merck West Point facility is listed as OAI. Therefore, the application is unapprovable. When approved, a 24 months expiry will be granted.

/S/ 7/14/1998

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/

7/14/98

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:

NDA 20-801
HFD-180/Division File
HFD-180/LTalarico
HFD-181/CSO/MFolkendt
HFD-180/AA1-Hakim
R/D Init by: EDuffy/7-13-98
AAH/dob F/T 7-14-98\WORD: c:\wordfiles\chem\N\20801806.2aa

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

21

J. C. -

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-801

CHEM. REVIEW #1 REVIEW DATE: 6/30/1997

NOV 13 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	12/18/1996	12/19/1996	01/10/1997
Amendment	04/10/1997	04/11/1997	04/11/1997
Amendment	05/30/1997	06/2/1997	06/19/1997
Amendment	10/09/1997	10/16/1997	10/24/1997

NAME & ADDRESS OF APPLICANT:

Merck Research Laboratories
Sumneytown Pike, BLA-20
West Point, PA 19486

DRUG PRODUCT NAME

<u>Proprietary:</u>	PEPCID® Acid Controller™
<u>Nonproprietary/USAN:</u>	Famotidine
<u>Code Name/#:</u>	MK-0208
<u>Chem. Type/Ther. Class:</u>	3S

PHARMACOL. CATEGORY/INDICATION:

Antagonist (to histamine H₂ receptors)/Prevention and Treatment of Heartburn

DOSAGE FORM:

Chewable Tablets

STRENGTHS:

10 mg

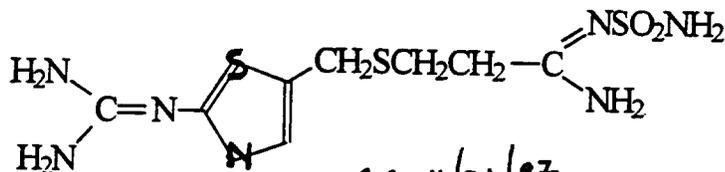
ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

_____ Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:
1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propylidene] sulfamide



AA 11/21/97

Molecular Formula: C₉H₁₃N₃O₂S₃

Molecular Weight: 337.43

SUPPORTING DOCUMENTS:

Document No. and holder name	Item to be reviewed	Notes
------------------------------	---------------------	-------

NDA 20-235 Merck	Famotidine tablets	Approved NDA
NDA 19-462 Merck	NDA (drug substance famotidine)	Approved NDA
NDA 20-752 Merck	NDA (Pepcid® RPD tablets)	Approved NDA

RELATED DOCUMENTS (if applicable):

NDA 19-462 (Tablets PEPCID® prescription strength)
 NDA 20-325 (Pepcid® AC Acid Controller™ Tablets)

CONSULTS: Stability data analysis consulted to Division of Biometrics (HFD-720)

REMARKS/COMMENTS: This NDA review concerns with the drug product. The drug substance has been reviewed and approved in previous NDAs (drug substance Famotidine).

CONCLUSIONS & RECOMMENDATIONS: The firm has to provide additional information/data regarding the following items:

- a. Holding time for the drug substance before shipping to the drug product manufacturing sites.
- b. Manufacturing of drug product in two different sites
- c. sampling plan for release testing
- d. Famotidine degradants
- e. Container/Closure system

An information request letter should be sent to the firm detailing the above queries and requesting appropriate responses. Approvable.

**APPEARS THIS WAY
ON ORIGINAL**

/S/ 11/13/1997
 Ali Al-Hakim, Ph.D.
 Review Chemist, HFD-180

/S/ 11/13/97
 Eric P. Duffy, Ph.D.
 Chemistry Team Leader, HFD-180

cc:
 NDA 20-801
 HFD-180/Division File
 HFD-180/LTalarico
 HFD-181/CSO/MFolkendt
 HFD-180/AAl-Hakim
 R/D Init by: EDuffy/11-10-97
 AAH/dob F/T 11-12-97/WP: c:\wpfiles\chem\N\20801706.1aa

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

PHARMACOLOGY REVIEW(S)

NDA 20,801

Sponsor and Address: Merck Research Laboratories
West Point, PA

JAN 17 1997

Date of Review: January 17, 1997

Date of Submission: December 19, 1996

Product Name: PEPCID Acid® Controller™

Generic Name: Famotidine

Dosage Form: Chewable Tablets 10 mg

Pharmacologic Category: Histamine H₂-receptor
antagonist/antiulcer agent

Composition:

<u>Ingredient</u>	<u>mg/tab</u>
Famotidine	10.00
Lactose	
Hydroxypropyl Methylcellulose	
Cellulose Acetate	
Hydroxypropyl Cellulose	
Mannitol	
Microcrystalline Cellulose	
Aspartame	
Magnesium Stearate	
Red Ferric Oxide	
Total Tablet Weight	

Indication: Prevention and treatment of heartburn.

Related NDAs: NDA 19,462 (PEPCID tablets, Merck)
NDA 20,325 (PEPCID AC tablets, Merck)

REVIEW AND EVALUATION OF PHARMACOLOGY
AND TOXICOLOGY DATA
Original Summary

SUMMARY AND EVALUATION:

This NDA provides for 10 mg PEPCID (famotidine) chewable tablets as an alternate dosage form to an already approved tablet as an OTC therapy for the prevention and treatment of heartburn. Pepcid is a well established approved therapeutic entity. Tablet, suspension and injectable forms of PEPCID have been approved for use in the treatment of active duodenal ulcer, active benign gastric ulcer and pathological hypersecretory conditions and in the maintenance therapy for duodenal ulcer patients after healing the ulcer. Since the drug has already been found to be safe and is the subject of 4 approved NDAs with extensive clinical exposure, there is no need for additional preclinical studies. Approval of this NDA is recommended by Pharmacology.

APPEARS THIS WAY
ON ORIGINAL

/S/

Jasti B. Choudary, Ph.D., B.V.Sc.
Pharmacology Team Leader

CC:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd

JBC/hw/1/17/97

C:\WPFILES\PHARM\N\20801701.0JC

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION (Stability Analysis)**NDA#:** 20-801**Date:** MAY - 7 1998**Applicant:** Merck Research Laboratories.**Name of drug:** Nonprescription Pepcid AC Acid Controller (famotidine) Tablets.**Documents reviewed:** Documents dated 2/5/1998 and data on a diskette submitted by the sponsor.**Chemist Reviewer:** Dr. Al-Hakim, HFD-180.

I. **Introduction:** In this NDA Supplement, the firm has requested an expiry period of 24 months for Pepcid AC Tablets when it is stored below or at 30 °C (protect from moisture).

II. **Design**

Number of package types: 4;**Package Configuration:****Number of Lots:** 3 lots for each package type;

Package Type	Lot ID.
PET	214525, 214563, and 214565
PAPER	214525, 214563, and 214565
STRIP1	214525, 214563, and 214565
STRIP2	214525, 214563, and 214565

Temperature: 25 °C/60% RH and 30 °C/60% RH.

Tested Parameters:

The tested parameters with regard to the Potency and Total Degradate analyzed by the sponsor are listed below.

Package Type	Tested Parameters*
PET	PONTENCY1, POTENCY2, TOTDEG1, and TOTDEG2
PAPER	PONTENCY1, POTENCY2, TOTDEG1, and TOTDEG2
STRIP1	PONTENCY1, POTENCY2, TOTDEG1, and TOTDEG2
STRIP2	PONTENCY1, POTENCY2, TOTDEG1, and TOTDEG2

*: PONTENCY1 and TOTDEG1 were tested at 25 °C/60% RH; POTENCY2 and TOTDEG2 were tested at 30 °C/60% RH.

Specification limits:

1. Potency (POTENCY1 and POTENCY2): 90% LC. - 110% LC. (Label Claim),
2. Total Degradate (TOTDEG1 and TOTDEG2): $\leq 1.5\%$.

Sampling Times: Except for the package type JVSTRIP1 tested at 30 °C/60% RH, the observation time points for the three lots (214525, 214563, and 214565) packaged with the four package types (PET, PAPER, STRIP1, and STRIP2) and stored at 25 °C/60% RH and 30 °C/60% RH were 0, 3, 6, 9, 12, and 18 months.

The observation time points for the three lots (214525, 214563, and 214565) packaged with JVSTRIP1 and tested at 30 °C/60% RH were 0, 3, 6, 9, and 12 months.

III. Stability Analysis

APPEARS THIS WAY
ON ORIGINAL

III.a: Statistical Methods

The sponsor analyzed Total Degradant data using the SAS program developed by the Division of Biometrics, FDA for both temperatures: 25 °C/60% RH and 30 °C/60% RH. The

procedures consist of the following two steps.

Step 1: Model selection (Test for pooling of stability batch data).

An assessment is made as to whether or not the degradation curves, considering all individual batches separately, are similar. If the degradation curves are similar, it is desirable to pool the data in order to obtain more precise estimates of expiration dating periods. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data, and applying statistical tests for equality of slopes and/or zero-time intercepts to these models. The following two conditions must be satisfied to allow such pooling of the data.

- a) The test of the hypothesis that a model with separate intercepts and separate slopes (H_1) fits the data better than a model with separate intercepts and common slope (H_0) should have a p-value of 0.25 or greater, (equality of slopes) and,
- b) The test of the hypothesis that a model with separate intercepts and the estimated common slope (H_1) fits the data better than a model with common intercept and common slope (H_0) should have a p-value of 0.25 or greater (equality of intercepts given parallel lines).

The rationale for using a p-value of 0.25 for tests of this nature is presented in the paper of Bancroft "Analysis and inference for incompletely specified models involving the use of preliminary test of significance", Biometrics, pp. 427-442 (1964).

At the end of step 1, one of the following models is selected for the degradation model,

- a) separate intercepts and separate slopes,
- b) separate intercepts and common slope,
- c) common intercept and common slope.

APPEARS THIS WAY
ON ORIGINAL

Step 2: Construction of the 95% lower, or 95% upper, or 95% two-sided confidence intervals for the mean degradation curve.

The 95% lower, or a 95% upper, or two-sided confidence intervals are constructed for the mean degradation curve based on model selected at step 1.

III.b: Acceptance criteria

APPEARS THIS WAY
ON ORIGINAL

In order to have an acceptable potency level of the assay under test, the 95% lower confidence bound should be above the lower specification limit and the 95% upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then either the 95% lower confidence bound should be above the lower specification limit or the 95% upper confidence bound should be below the upper specification limit.

III.c: Data analysis and results

This reviewer estimated the expiration dates by applying the SAS program developed by the Division of Biometrics, FDA to Potency data submitted by the sponsor for both temperatures (25 °C/60% RH and 30 °C/60% RH), using two-sided confidence intervals. The expiration dates of the tested parameters with regard to Potency estimated by this reviewer and Total Degradants estimated by the sponsor for each of the two temperatures, are presented in Table 3.1.

Table 3.1 Estimated Expiration Dates Of the Tested Parameters

Package Type: PET

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	27
TOTDEG1	72
POTENCY2	30
TOTDEG2	72

APPEARS THIS WAY
ON ORIGINAL

Package Type: PAPER

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	49
TOTDEG1	72
POTENCY2	26
TOTDEG2	72

APPEARS THIS WAY
ON ORIGINAL

Package Type: STRIP1

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	56
TOTDEG1	72
POTENCY2	48
TOTDEG2	48

APPEARS THIS WAY
ON ORIGINAL

Table 3.1 Estimated Expiration Dates Of the Tested Parameters
(Continued)

Package Type: STRIP2

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	49
TOTDEG1	72
POTENCY2	28
TOTDEG2	72

IV. Reviewer's Summary

Based on the results of the stability analyses and the conservative principle (choosing the shortest estimated expiration dates over the tested parameters within each package type), the expiration dates for each of the four Package Types are summarized in Table 4.1.

Table 4.1 (Reviewer's) The estimated expiration dates for the four Package Types

Package Type	Estimated Expiration Date (Month)
PET	27
PAPER	26
STRIP1	48
STRIP2	28

Table 4.1 indicates that data support an expiration date of 24 months for the four package Types, PET, PAPER, STRIP1, STRIP2, stored at room temperature 25°C/60% RH and 30 °C/60% RH.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/S/

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Sankoh

/S/

Dr. Welch

/S/

5/7/98

- cc: Original NDA# 20-801
- HFD-180/Dr. Talarico
- HFD-180/Dr. Al-Hakim
- HFD-180/Mr. Folkendt
- HFD-720/Dr. Welch
- HFD-720/Dr. Sankoh
- HFD-720/Dr. Chen
- HFD-720 File Copy

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION

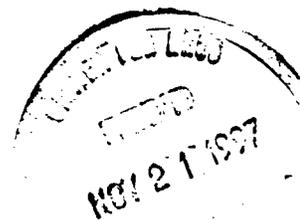
NDA#: 20-801

Date: November 20, 1997

Applicant: Merck Research Laboratories.

Name of drug: Pepcid AC Chewable.

Documents reviewed: Documents dated 2/24/1997, 10/20/1997, and 11/17/1997. Data on a diskette submitted by the sponsor.



I. Introduction: In this NDA Supplement, the firm has requested an expiry period of 36 months when the product is stored below 30 °C.

In this stability study, data from the following six folders were submitted: .PAPER, .PET, PAPER, PET, STRIP1, and STRIP2. For each of the six folders, Dr. Al-Hakim, the reviewing chemist, and this reviewer have requested the firm to perform the statistical analysis to estimate the expiration dates on each of the following tested parameters with respective to Potency and Total Degradate: 1. Potency - POTENCY1, POTENCY2, POTENCY3, and POTENCY4; 2. Total Degradate - TOTDEG1, TOTDEG2, TOTDEG3, and TOTDEG4. However, the sponsor only estimated the expiration dates of the tested parameters with stored temperature below (less than or equal to) 30 °C for each of the six folders. The stability review for each of the six folders will be based on the expiration dates of the tested parameters estimated by the firm.

II. Design

Number of package types: 4;

Package Configuration:

Number of Lots: 3 lots for each package type;

Package Type	Lot ID.
PAPER	044B002, 044B003, and 044B004
PET	044B002, 044B003, and 044B004
PAPER	214525, 214563, and 214565
PET	214525, 214563, and 214565

APPEARS THIS WAY
ON ORIGINAL

Tested Parameters:

The tested parameters with regard to the Potency and Total Degradate analyzed by the sponsor are listed below.

Package Type	Tested Parameters
PAPER	POTENCY1 and TOTDEG1
PET	POTENCY1 and TOTDEG1
PAPER	POTENCY1, POTENCY2, TOTDEG1, and TOTDEG2
PET	POTENCY1, POTENCY2, TOTDEG1, and TOTDEG2

APPEARS THIS WAY
ON ORIGINAL

Temperature: Less than or equal to 30 °C

APPEARS THIS WAY
ON ORIGINAL

Specification limits:

1. Potency (POTENCY1 and POTENCY2): 90% LC. - 110% LC. (Label Claim),
2. Total Degradate (TOTDEG1 and TOTDEG2): ≤ 1.5%.

Sampling Times: For temperature less than or equal to 30°C, the observation time points for each lot by package type are listed below.

APPEARS THIS WAY
ON ORIGINAL

Package Type .PAPER

LOT ID.	Observed Time Points (Week)
044B002	0, 21, 56, 80, 106, and 158.
044B003	0, 18, 29, 54, 79, 103, and 157.
044B004	0, 18, 29, 54, 79, 103, and 157.

Package Type: .PET

LOT ID.	Observed Time Points (Week)
044B002	0, 21, 56, 80, 106, and 158.
044B003	0, 17, 29, 53, 78, and 102.
044B004	0, 17, 29, 53, 78, 102, and 157.

Package Type: PAPER

LOT ID.	Observed Time Points (Month)
214525	0, 3, and 6.
214563	0, 3, and 6.
214565	0, 3, and 6.

Package Type: PET

LOT ID.	Observed Time Points (Month)
214525	0, 3, and 6.
214563	0, 3, and 6.
214565	0, 3, and 6.

III. Sponsor's Analysis

APPEARS THIS WAY
ON ORIGINAL

III.a: Statistical Methods

The sponsor analyzed the stability data using the SAS program developed by the Division of Biometrics, FDA. The procedures consist of the following two steps.

Step 1: Model selection (Test for pooling of stability batch data).

APPEARS THIS WAY
ON ORIGINAL

An assessment is made as to whether or not the degradation curves, considering all individual batches separately, are similar. If the degradation curves are similar, it is desirable to pool the data in order to obtain more precise estimates of expiration dating periods. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data, and applying statistical tests for equality of slopes and/or zero-time intercepts to these models. The following two conditions must be satisfied to allow such pooling of the data.

- a) The test of the hypothesis that a model with separate intercepts and separate slopes (H_1) fits the data better than a model with separate intercepts and common slope (H_0) should have a p-value of 0.25 or greater, (equality of slopes) and,
- b) The test of the hypothesis that a model with separate intercepts and the estimated common slope (H_1) fits the data better than a model with common intercept and common slope (H_0) should have a p-value of 0.25 or greater (equality of intercepts given parallel lines).

The rationale for using p-value of 0.25 for tests of this nature is presented in the paper of Bancroft "Analysis and inference for incompletely specified models involving the use of preliminary test of significance", Biometrics, pp. 427-442 (1964).

At the end of step 1, one of the following models is selected for the degradation model,

- a) separate intercepts and separate slopes,
- b) separate intercepts and common slope,
- c) common intercept and common slope.

APPEARS THIS WAY
ON ORIGINAL

Step 2: Construction of the 95% lower, or 95% upper, or 95% two-sided confidence intervals for the mean degradation curve.

The 95% lower, or a 95% upper, or two-sided confidence intervals are constructed for the mean degradation curve based on model selected at step 1.

III.b: Acceptance criteria

In order to have an acceptable potency level of the assay under test, the 95% lower confidence bound should be above the lower specification limit and the 95% upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then either the 95% lower confidence bound should be above the lower specification limit or the 95% upper confidence bound should be below the upper specification limit.

APPEARS THIS WAY
ON ORIGINAL

III.c: Data analysis and results

The expiration dates of the tested parameters with regard to Potency and Total Degradate estimated by the sponsor for each of the four package types are demonstrated in Table 3.1 (below).

Table 3.1 (Sponsor's) Estimated Expiration Dates Of the Tested Parameters

Package Type: PAPER

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	84
TOTDEG1	84

APPEARS THIS WAY
ON ORIGINAL

Package Type: PET

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	84
TOTDEG1	84

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 3.1 (Sponsor's) Estimated Expiration Dates Of the Tested Parameters
(Continued)

Package Type: PAPER

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	24
POTENCY2	10
TOTDEG1	24
TOTDEG2	24

Package Type: PET

Tested Parameters	Estimated Expiration Date (Month)
POTENCY1	13
POTENCY2	12
TOTDEG1	24
TOTDEG2	24

APPEARS THIS WAY
ON ORIGINAL

IV. Reviewer's Summary

Based on the results of the sponsor's analyses and the conservative principle, the expiration dates for each of the four Package Types are summarized in Table 4.1 (Below).

Table 4.1 (Reviewer's) The estimated expiration dates for the four Package Types

Package Type	Estimated Expiration Date (Month)
PAPER	84
PET	84
PAPER	10
PET	12

APPEARS THIS WAY
ON ORIGINAL

Table 4.1 indicates that the data support an expiration date of 36 months for the two Package Types, PAPER and PET, under the room temperature 30°C and Ambient Relative Humidity. However, data from the other two Package Types, PAPER and PET, do not support an expiration date of 36 months, under the room temperatures 25°C/60% Relative Humidity and 30°C/60% Relative Humidity.

APPEARS THIS WAY
ON ORIGINAL

/S/

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Sankoh

/S/

11/20/97

APPEARS THIS WAY
ON ORIGINAL

Dr. Smith

- cc: Original NDA# 20-801
- HFD-180/Dr. Talarico
- HFD-180/Dr. Al-Hakim
- HFD-180/Mr. Folkendt
- HFD-720/Dr. Smith
- HFD-720/Dr. Sankoh
- HFD-720/Dr. Chen
- HFD-720 File Copy

APPEARS THIS WAY
ON ORIGINAL